

NIH COMMON FUND HIGH-RISK HIGH-REWARD RESEARCH SYMPOSIUM

December 15 – 17, 2014

SPEAKER ABSTRACTS – DAY 2 (DEC. 16, 2014)

The Reductive Stress Hypothesis and the Antioxidant Treatment Paradox

Awardee: Ivor J. Benjamin

Award: Pioneer Award

Awardee Institution: Medical College of Wisconsin

The reductive stress hypothesis in disease pathology was recently revisited by Benjamin and colleagues who have demonstrated that a protein-misfolding (R120G CryAB) cardiomyopathy was under reductive stress, as opposed to oxidative stress, from an over-active antioxidative system. Decreasing the function of glucose-6-phosphate dehydrogenase (G6PDH), which generates the reductant NADPH, “cures” the disease in a mouse model by ameliorating reductive stress, aggresome formation, hypertrophy, heart failure and death. Since this discovery, several laboratories have independently implicated the effects of reductive stress as causal mechanisms in hyperglycemic-induced metabolic syndrome, experimental ischemic injury (e.g., dominant negative Nox4 isoform), cardiomyopathy, and inheritable skeletal and cardiac myopathy. Of direct translational relevance, carriers of the Gd-Mediterranean allele of G6PD deficiency living on coastal island in Sardinia, Italy are remarkably protected against ischemic heart disease, cerebrovascular strokes, retinal vein occlusion (RVO), nonarteritic anterior optic neuropathy (NAION), and perhaps, diabetic retinopathy, underscoring the farreaching implications of this work in humans.

An alternative to the reductive stress hypothesis has been extensively pursued for almost five decades, beginning with the oxidative stress theory of aging, on the basis that free radicals and reactive oxygen species (ROS), the byproducts of oxidative phosphorylation, are deleterious in the setting of inadequate ROS scavenging by the antioxidative system. Oxidative stress has been proposed as a major mediator of vascular dysfunction, and has been proposed as a pathological factor in almost every disease from glucotoxicity in pancreatic β -cells, inflammation in infection, cancer metastasis and survival, liver fibrosis, neurodegenerative disease. Stroke, (not ‘classic’ neurodegenerative), affects 141 million people worldwide in 2012. Thousands of preclinical and clinical studies over the decades have been inconclusive and failed to show efficacy of antioxidant therapeutics while other trials were prematurely terminated owing increased morbidity and mortality. What has not been clear are what factor(s) might account for such abysmal failure. Both proponents and opponents of oxidative stress have fueled the confusion and controversy—and both sides have overlooked the importance of “reductive stress,” as opposed to oxidative stress, as a causal mechanism in disease pathogenesis. What are the factor(s) that might increase the susceptibility for major adverse toxicity and fatal outcomes from antioxidant therapy? We postulate that either pro-reducing redox state among heterogeneous clinical cohorts and/or the pro-reducing effects of antioxidants agents will, either alone or combinatorially, promote life-threatening reductive stress. Antioxidant therapeutics *per se* are not the culprits unless indiscriminately administered without regard for their biological context and/or consequence across the redox spectrum. Moreover, we think that the rationale for the similar use of current compounds in antioxidant clinical trials are seriously flawed and are unlikely to answer or overcome the existing deficiencies and major barriers in the field. Understanding the mechanism for basic redox reactivity and for biological

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redox effects is a *sine qua non* for the rational design of clinical trials using targeted oxido-reductive therapeutics in disease pathology.